Study Title	A PHASE I/II CLINICAL TRIAL TO DETERMINE SAFETY AND FEASIBILITY OF USING AN ACELLULAR AMNIOTIC FLUID APPLICATION TO EXPEDITE HEALING IN CHRONIC WOUNDS
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1- SYNOPSIS

Title	A phase I/II clinical trial to determine safety and feasibility of using an acellular human amniotic fluid (pAF) application to expedite healing of chronic wounds
Short Title	pAF for the Treatment of Chronic Wounds
IRB Number	IRB_00128708
IND	IND # 19330
Phase	Phase I/II
Design	This is a prospective randomized controlled study to determine the safety and feasibility of using processed sterile filtered amniotic fluid (pAF) to expedite healing in chronic wounds.
Study Duration	4 years
Study Center(s)	University of Utah
Objectives	Primary Objective: • To determine the safety of using processed amniotic fluid (pAF) to treat patients with chronic wounds. Secondary Objective: • To determine efficacy by examining a reduction in wound size after application of pAF compared to Standard of Care (SOC).
Number of Subjects	60 patients
Diagnosis and Main Eligibility Criteria	Inclusion: 1. Patients 18-85 years old. 2. Patients with chronic upper and/or lower extremity wounds (including thermal) that are greater than 3 months, but less than 12 months old. 3. Patients with full thickness wounds. 4. Patients with at least one wound that is ≥ 5 cm^2 and <75 cm^2 in size. 5. Patient who is able to complete required site study visits and procedures in good faith Exclusion: 1. Patients admitted to the hospital at the time of enrollment. 2. Patients who are pregnant, nursing or plan to become pregnant while participating in the study. If of child-bearing potential, unwillingness to use effective birth control while participating in the

	study. 3. Suspicion of or diagnosis of osteomyelitis underlying the wound. 4. Patients who have received an investigational agent or intervention within the prior 30 days or plan to use within the study period. 5. Patient with sinus tracts, enterocutaneous fistulas or other epithelialized tracts. 6. Patients who require skin grafting. 7. Patients diagnosed with a highly disruptive, non-controlled mental health disorder (e.g.., bipolar, or schizophrenia. 8. Patients with a history of prior drug abuse.
Study Product, Dose, Route, Regimen	pAF will be delivered to the clinic on the date of application. Dose is 1ml/5cm^2; Route: injected directly into wound; Limited to two injections.
Statistical Methodology	The primary goal of the analysis is to demonstrate safety, which does not require statistical significance. The secondary goal of the analysis is to assess efficacy by comparing percent reduction in wound area. Additional exploratory analyses will be conducted, such as subgroup analyses.

2- OBJECTIVES

-Primary Objective:

- The Burn Outpatient Clinic sees multiple types of wounds from burn to non-burn. The care of patients with chronic wounds is complex and difficult. To date, we have not found any treatments, including various dressings or other stem cell based therapies, which consistently reduce time of wound closure and improve pain. We would like to investigate the safety of using pAF to treat these wounds.

-Secondary Objective:

- We would like to determine efficacy of using pAF to treat chronic wounds by examining a reduction in wound size after application of pAF compared to Standard of Care (SOC).

3- ENDPOINTS

-Primary Endpoint:

- Whether the patient experienced any post-randomization, study-related SAEs while on study (up to Visit 5, defined later).

-Secondary Endpoint:

- The percent reduction in wound area at Visit 5 relative to the size at randomization visit.

4- BACKGROUND AND RATIONALE

The Burn Outpatient Clinic patient demographic includes 7-10% non-burn wounds per month. These wounds range from chronic venous stasis ulcers, pressure ulcers, diabetic foot ulcers, to rare genetically predisposed wounds. These wounds are slow to heal, they require large amounts of health care resources, and cause disability for the patient. We have yet to find a standard treatment modality or wound care regimen that consistently lessens time to wound closure, improves pain, and reduces scarring.

Human amniotic fluid and amniotic membrane have been used for many years in regenerative medicine. Literature review shows that amniotic fluid with the cellular components included [1, 2] and an additional study using granulized amniotic membrane with amniotic fluid have shown improved wound healing rates in select populations [3]. Amniotic fluid contains cytokines, nutrients, and growth factors that are required for development of the fetus. Components of the amniotic fluid that make it important to wound healing include its anti-inflammatory properties (38%), immune regulation (25%) and anti-microbial properties (9%) [4].

While amniotic membranes have been used for over 100 years in burns and other chronic wounds, amniotic fluid has not been rigorously studied. With the continuous rise of healthcare costs, price is another factor to consider with amniotic fluid and membranes. It is reported that the US spends more than 25 billion dollars annually on chronic wounds [5]. This is on the rise due to the aging of the population and increases in obesity and diabetes. In an article titled " Wound Care Outcomes and Associated Costs Among Patients Treated in US Outpatient Wound Centers: Data from the US Wound Registry", it was estimated that the mean healing cost per wound ranged from $3,927-$9,358 depending on the type of wound [6]. In other words, on average 2.6 - 6.3 million people require treatment for chronic wounds annually, a heavy toll for national healthcare costs.

The goal of our study is to assess, in an outpatient setting, the safety and healing in chronic wounds treated with pAF. We will include patients with upper or lower extremity full thickness wounds (including thermal) that are greater than 3 months old and less than 12 months old and who are able to complete required site study visits and procedures in good faith. The wound size must be greater than or equal to 5cm^2 and less than 75 cm^2. We will exclude anyone that is admitted to the hospital at the time of enrollment, is less than 18 years old or older than 85 years old, is known to be pregnant or planning to become pregnant (including women of childbearing potential who are unwilling to use effective birth control while participating in the study), is breastfeeding, has suspicion of osteomyelitis, has received or plans to receive an investigational agent or intervention, requires skin grafting, has wounds with sinus tracts, has a diagnosed highly disruptive uncontrolled mental health disorder, or has a known history of prior drug abuse. Our primary objective is to determine

the safety of using pAF to treat patients with chronic wounds and our secondary objective is to assess the reduction in wound size after application of pAF compared to standard of care.

Cases #1 & 2 show preliminary results that we have obtained with pAF applications when applied to refractory chronic wounds (>12 months without healing).

Case #1

A patient with a Martorell's ulcer with tendon exposure received 4 injections of pAF (Fig. 3A). The first injection consisted of 8 mL of pAF (Fig. 3B).

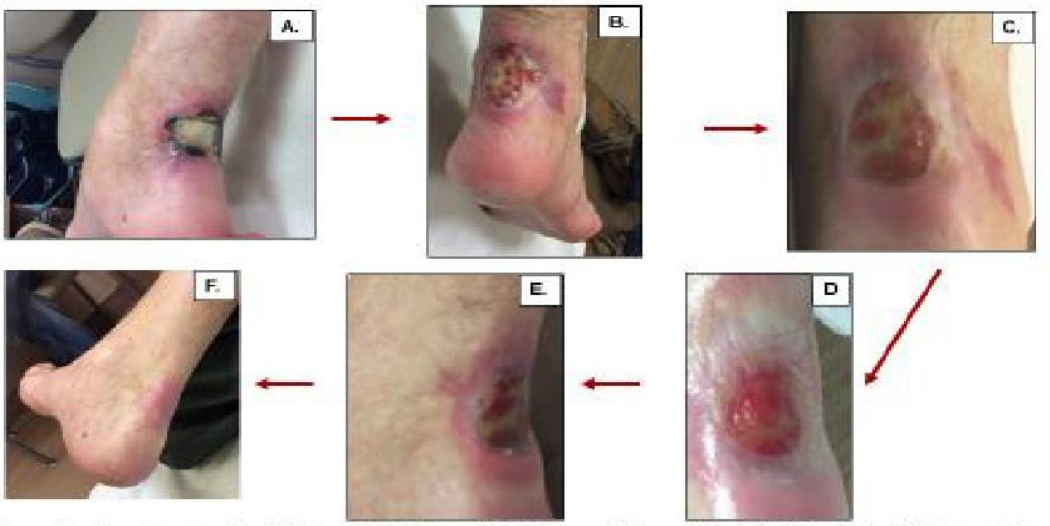

Figure 3. Treatment of a Martorell's ulcer with Processed Amniotic Fluid (pAF). A) Untreated chronic wound. B) The first injection consisted of 8 mL of pAF. C) A second injection of 9 mL of pAF. D) A third injection of 9 mL of pAF. E) A fourth injection of 9 mL pAF. F) Approximately 4 months after the first injection there was no tendon exposure and the wound had re-epithelialized.

Approximately, 1 month later, the patient received a second injection of 9 mL of pAF (Fig. 3C). Subsequent injections of 9 mL of pAF were given at approximately 2 and 4 months after the initial injection of pAF (Fig. D & E). Four months after the first pAF injection, there was no tendon exposure and re-epithelialization of the wound was apparent.

Case #2

A patient was involved in a bombing terrorist attack and sustained the following injuries: a 35% TBSA burn to the left leg, right leg, right hand, and posterior scalp; traumatic pseudoaneurysm of left popliteal artery; left fibular fracture; and left calcaneal fracture. He developed multiple infections of the left lower leg and heel including mucormycosis infection. He eventually healed however, 1 year from his injury and definitive treatment, a heel and Achilles non-healing post-traumatic ulcer persisted. He underwent traditional local

wound care strategies and peripheral vascular evaluation. The ulcers were open for greater than 1 year without evidence of healing.

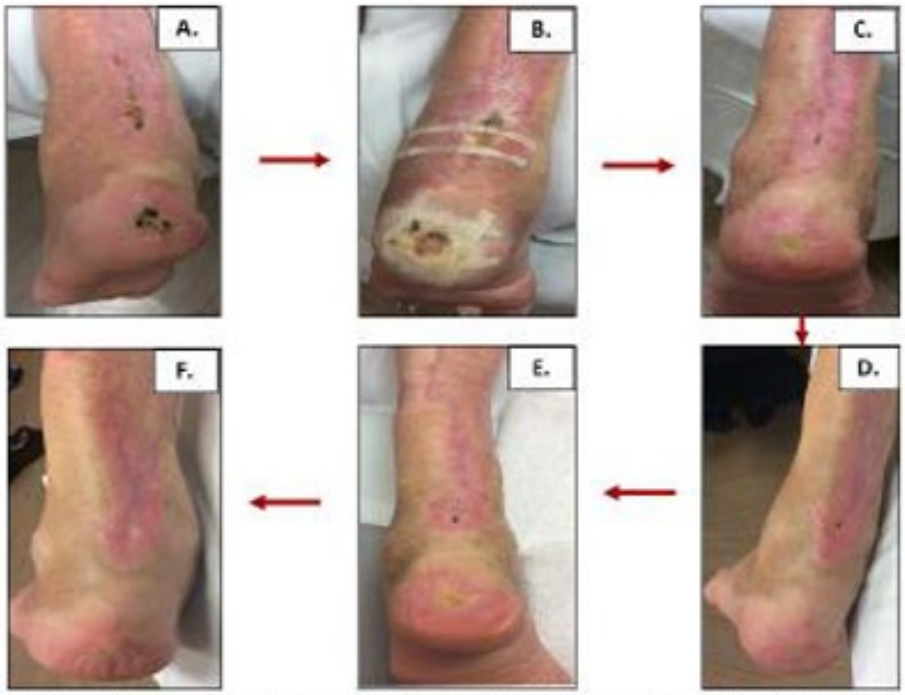

Fig. 4. Treatment of a chronic wound with pAF. A.) The first wound treatment with pAF B.) Second pAF treatment C.) Third pAF injection, plus amnion membrane application. D.) Debridement of the wound, followed by pAF injection plus amnion membrane application. E.) Reopening of wound after ortho procedure, repeated pAF injection. F.) Approximately 3 months after the first injection, the wound had completely healed.

He underwent eight amniotic fluid treatments within 1 year (Fig. 4). His wound was completely healed after seven treatments within 9 months (Fig. 4D). Unfortunately, he underwent another orthopedic procedure with prolonged casting of the left leg and suffered breakdown of the heel ulcer (Fig. 4E) requiring subsequent amniotic fluid injection to complete healing (Fig. 4F).

Amniotic fluid (AF): Preclinical Data

Early after conception and until the mother's water breaks for the delivery of their infant, the fetus is bathed in amniotic fluid. AF functions as a supportive cushion to the fetus and provides a protective environment. AF is a rich source of nutrients, cytokines and growth factors that are required for fetal development and maturation [7]. AF also contains stem cells with the potential to differentiate along multiple cell lineages [8, 9]. The protective and regenerative properties of AF are achieved via the exchange of water and solutes with surrounding tissues. This is accomplished via the utilization of different pathways during the course of a pregnancy that likely contribute to changes in the composition of the AF with gestational age[7].

Early reports showing that concentrates of AF inhibit the development of peritonitis were among some of the first evidence that AF has protective biological properties [10]. This was followed by a publication by Shimberg and co-workers that AF accelerates defense-repair mechanisms within damaged joints [10, 11]. Since these early publications, more sophisticated evaluations have revealed the presence of antimicrobial, immunomodulatory, and growth-promoting activities in AF [7], some of which are likely to contribute to its protective biological properties.

Reports about the antimicrobial activity of AF differ among investigators [12]. It is reported that AF with low antimicrobial activity is associated with a high incidence of an infectious syndrome in pregnant women [13]. Some studies show that AF is inhibitory, while others show no effect against the same microorganisms. Components with antimicrobial, antiviral and antifungal activity that are present in AF include lysozyme, peroxidase, transferrin, β-lysin, immunoglobulins and zinc-peptide complexes [12].

Immunomodulatory properties of AF are evident from studies showing that enteral feeding of AF suppresses the pro-inflammatory responses in preterm pigs with necrotizing enterocolitis [14]. Growth promoting activities of AF are supported by animal studies as well as by in vitro studies. These studies show that AF can enhance neochondrogenesis [15], regenerate peripheral nerves [16] and bone [17], accelerate re-epithelialization in corneas [18], and promote healing of human skin wounds [19]. Some of the factors that are found in AF that may contribute to these activities could be inflammatory mediators that include, but are not limited to TNF-a, IL-6, IL8, and IL-10 [20], trophic factors that include EGF, IGF-1, FGF, HGF and TGF-a [21-25], and HA (hyaluronic acid), an important factor in promoting re-epithelialization in human skin wounds [19].

Based on the hypothesis that nutrients, cytokines and growth factors contained in the non-cellular fraction of AF are useful for reparative and regenerative treatments in patients, Pierce et al. conducted a study at the University of Utah to address three issues [4]. The first was to determine the feasibility of consenting and screening volunteer donors for the routine collection of AF from full-term pregnant women who were scheduled for Caesarean sections (C-sections), and to then process the AF for clinical application. The second aim was to develop a processing method that resulted in a cell-free AF preparation suitable for clinical application. The third goal was to gain a better understanding of the components of the processed AF (pAF).

Goal #1: AF was collected by the staff of the Department of Obstetrics/Gynecology at the University of Utah hospital and was processed by technical staff of the Cell Therapy and Regenerative Medicine (CTRM) facility at the University of Utah. Physician-executed abdominal incisions were performed through the abdominal and uterine muscles without cutting into the amnion membrane. Using a sterile suction catheter connected to a sterile MediVac suction container (Cardinal Health, Waukegan, IL), a blunt end insertion with the catheter was made through the amniotic membrane and the AF aseptically suctioned into the MediVac container. The container was labeled, wrapped in frozen Insul-ice mats (Fisher Scientific, Hanover Park, IL) and placed in a temperature-monitored shipper that was

validated for transport between 2- 8 °C. The AF was transported to the CTRM facility at the University of Utah. Upon arrival at the CTRM facility, the tissue was immediately placed into a refrigerator at 2–8 °C until processing occurred.

Goal #2: At the time of processing, the MediVac container with AF was aseptically placed in a biological safety cabinet and the AF was aseptically transferred into sterile centrifuge tubes. The total volume and gross appearance of the AF were recorded and samples removed for sterility testing, cell counts and other relevant testing. The AF was centrifuged, the supernatant was collected, and the AF underwent a proprietary filtration process to eliminate insoluble components and sterilize the AF. The resulting product, processed AF (pAF), was evaluated for total volume, fluid chemistry, total protein, and hyaluronic acid (HA) levels. Final pAF products were also assessed for their cellular content and protein profiles using quantitative antibody arrays.

To validate the above described approach for collecting (Goal #1) and processing (Goal #2) AF, 36 pregnant women consented and passed the donor screening criteria. AF was successfully collected and processed from 17 of these individuals. Median AF volumes were 70 mL (range 10–815 mL; n = 17) [4].

Goal #3: Fluid chemistries were similar among the 17 pAFs, but some differences were noted in HA levels and cytokine profiles. Cytokine arrays revealed that an average of 304 ± 20 ng/mL (mean ±SD; n=3) of 400 proteins tested were present in pAF, with a majority of cytokines associated with host defense. Some of the peptides encountered and classified according to their function are found in table 1.

Table 1. A sampling of the proteins/peptides by annotation that we have identified in pAF

Pro-inflammatory	OPN, PAI-I, CD163, RAGE, IL17, IL1R3
Host defense	IL-27, LAG-3, GITR, PD1
Innate Immunity	Galectin-3, TLR-2, Osteoactivin
Antimicrobial	TSP-1, lactoferrin, CXCL14, Trappin-2, CCL-28, MIG
Anti-inflammatory	IL1-ra, MBL
Embryonic development	DKK1, DKK3
Angiogenesis	VEGF R1, Transferring, TIMP-2
Wound healing	OPN, PAPP-A, FAP

Experience with using pAF in Clinical Settings:

pAF manufactured at the University of Utah has been clinically used in over 2000 applications for over 100 different conditions. A majority of treatments have been for wounds and burns. No unexpected and related adverse events have been directly associated with the injection or topical application of pAF in these previous uses (Table 2).

Table 2. Number and Type of Clinical Applications that were treated with Processed Amniotic Fluid

Description	Number of Applications
Burns (All anatomical areas, 2nd & 3rd Degree)	736
Wounds (Chronic, Acute, Ulcers, Necrotizing Fascitis, etc.)	949
Urology (urethral stricture, pyronies, etc.)	177
Orthopedics (Joints, tendonitis, tendon tears, carpel tunnel, etc.)	188
Spine (cervical, lumbar, sacral)	43
Occular (GVHD, dry eye)	101
GI (Strictures, Fistulas,)	50
TMJ (joint arthritis)	30
Neuropathy (nerves)	7
Other	50
Total	**2331**

ELIGIBILITY CRITERIA

Inclusion Criteria:

1. Patients who are 18-85 years old
2. Patients with chronic upper and/ or lower extremity wounds (including thermal) that are greater than 3 months, but less than 12 months old
3. Patients with full thickness wounds
4. Patients with at least one wound that is ≥5 cm^2 and <75 cm^2 in size
5. Patient who is able to complete required site study visits and procedures in good faith.

Exclusion Criteria:

1. Patients admitted to the hospital at the time of enrollment
2. Patients who are pregnant, nursing or plan to become pregnant while participating in the study. If of child-bearing potential, unwillingness to use effective birth control while participating in the study.
3. Suspicion of or diagnosis of osteomyelitis underlying the wound.
4. Patients who have received an investigational agent or intervention within the prior 30 days or plan to use within the study period.
5. Patient with sinus tracts, enterocutaneous fistulas or other epithelialized tracts
6. Patients who require skin grafting
7. Patients diagnosed with highly disruptive, non-controlled mental health disorder (e.g. bipolar, or schizophrenia.
8. Patients with a history of prior drug abuse

5- STUDY DESIGN AND PROCEDURES

A written Informed Consent will be obtained from all subjects before any study-related procedures are executed. Subjects will be randomized into two groups at a 1:1 ratio. The randomization will employ random block sizes to limit the ability to predict the next subject's

treatment prior to randomization. Because of the random block sizes, it is not guaranteed that exactly 30 subjects will be randomized to each arm. There may be as few as 28 in the treatment arm (32 in the control arm) or as many as 32 in the treatment arm (28 in the control arm). Because of the modest number of overall patients and the anticipated slow accrual rate, stratification will not be used in the randomization procedure.

If a subject has more than one qualifying wound, the largest wound will be randomized to one of the two study arms (pAF or SOC) and included in the primary and secondary endpoint analyses. All other wounds will be treated with standard of care.

Whether a wound is randomized to pAF or SOC, many of the components of the treatment regimen are the same. The overall treatment is described, with differences unique to the pAF arm emphasized.

- Study Overview:
  a. Visit 1:
     i. Screening of subject and wounds for eligibility
     ii. Informed consent
     iii. Pregnancy Test (only applicable to women of childbearing potential)
     iv. Subject/Wound evaluation and assessment including measurements (includes local cleansing and debridement if needed, digital image capture, manual measurements, and maximal wound depth)
     v. Wound-associated pain assessment
     vi. Laboratory tests:
        1. Parvovirus B19 serology and nucleic acid testing
        2. Complete blood count including platelet count with white blood cell (WBC) differential
        3. Chemistry panel to include aminotransferases, serum creatinine
        4. Hemoglobin A1c
        5. HLA Type 1 antibody (Only done on the first 10 patients enrolled)
        6. PT/INR
        7. PTT
        8. Wound cultures
     vii. Standard Burn Center wound care treatment
     viii. Schedule subject's next visit to occur within 6 weeks (+/- 1 week) of consent

If a subject's wound reduces in size greater than or equal to 50% between Visit 1 and Visit 2, or if the subject received any out-of-study investigational agent/intervention to the wound after Visit 1 but before Visit 2, the subject will not be randomized into the study and will be excluded. Because such subjects are not to be randomized, they are not considered enrolled and do not count towards the target enrollment of 60 subjects.

  b. Visit 2 (6 weeks +/- 1 week from Visit 1):

i. Subject/Wound evaluation and assessment including measurements (includes local cleansing and debridement if needed, digital image capture and upload to the Burn Unit image storage, manual measurements, and maximal wound depth)
ii. Wound-associated pain assessment
iii. Wound cultures
iv. Determination of whether largest qualifying wound is eligible for randomization (see note following Visit 5)
v. If applicable, randomization of largest qualifying wound to pAF or SOC arm

If in pAF arm,

1. The amount of processed amniotic fluid to be injected into the randomized wound will be calculated based on the area of the wound (1ml/5cm^2).
2. To assist with discomfort, topical or injectable anesthetic will be applied to the wound based on standard dosing recommendations. Pliaglis (Lidocaine 7%, tetracaine 7%; emulsion cream) is the topical anesthetic applied 30-45 min prior to procedure in the clinic setting. If this is insufficient we will inject 1% lidocaine directly into the study site. All dosing is based on weight based recommendations in adults. Some patients may not need any of the above and some may require all.
3. The wound will be cleansed and debrided if needed prior to application of pAF and then prepped with chloraprep.
4. pAF is thawed and drawn into a 10ml syringe and, using a 25g needle, injected into the wound.
5. pAF is injected at the skin-wound base interface and base of the wound in a grid pattern (approximately 0.1 ml of pAF spaced evenly apart throughout the wound).
6. Standard burn center wound treatment regimen is applied to the wound per standard dressing care procedures (see *Standard Burn Center Wound Treatment Regimen* below).

vi. Standard Burn Center wound care treatment of all other wounds (if any), including the wounds randomized to standard of care.
vii. Schedule subject's next visit to occur 6 weeks (+/-1 week) later.
viii. Subject will receive a follow-up phone call within 24 hours AND 5-7 days after visit to identify any adverse events that occur in relation to study participation and

record additional medications that were taken.

c. Visit 3 (6 weeks +/- 1 week from Visit 2):
   i. Subject/Wound evaluation and assessment including measurements (includes local cleansing and debridement if needed, digital image capture and upload to the Burn Unit image storage, manual measurements, and maximal wound depth)
   ii. Wound-associated pain assessment
   iii. Wound cultures

If in pAF Arm

1. The amount of processed amniotic fluid to be injected into the randomized wound will be calculated based on the area of the wound (1ml/5cm^2).
2. To assist with discomfort, topical or injectable anesthetic will be applied to the wound based on standard dosing recommendations. Pliaglis (Lidocaine 7%, tetracaine 7%; emulsion cream) is the topical anesthetic applied 30-45 min prior to procedure in the clinic setting. If this is insufficient we will inject 1% lidocaine directly into the study site. All dosing is based on weight based recommendations in adults. Some patients may not need any of the above and some may require all.
3. The wound will be cleansed and debrided if needed prior to application of pAF and then prepped with chloraprep.
4. pAF is thawed and drawn into a 10ml syringe and, using a 25g needle, injected into the wound.
5. pAF is injected at the skin-wound base interface and base of the wound in a grid pattern (approximately 0.1 ml of pAF spaced evenly apart throughout the wound).
6. Standard burn center wound treatment regimen is applied to the wound per our standard dressing care procedures (see *Standard Burn Center Wound Treatment Regimen* below).

   iv. Standard Burn Center wound care treatment of all other wounds if any, including the wounds randomized to standard of care
   v. Collect information on adverse events related to study participation.
   vi. Schedule subject's next visit to occur 6 weeks (+/-1 week) later.
   vii. Subject will receive a follow-up phone call within 24

hours AND 5-7 days after visit to identify any adverse events that occur in relation to study participation and record additional medications that were taken.

d. Visit 4 (6 weeks +/-1 week from Visit 3):
    i. Subject/Wound evaluation and assessment including measurements (includes local cleansing and debridement if needed, digital image capture and upload to the Burn Unit image storage, manual measurements, maximal wound depth)
    ii. Wound-associated pain assessment
    iii. If the wound(s) remains open, Standard Burn Center wound care treatment
    iv. Laboratory tests:
        1. Parvovirus B19 serology and nucleic acid testing for subjects testing negative for Parvovirus at Visit 1.
        2. Complete blood count including platelet count with WBC differential
        3. Chemistry panel to include aminotransferases, serum creatinine
        4. Hemoglobin A1C
        5. HLA Type 1 antibody (Only done on the first 10 patients enrolled)
        6. PT/INR
        7. PTT
        8. Wound cultures
    v. Collect information on adverse events related to study participation.
    vi. Schedule the final study visit, 3 months (+/- 1 week) later.

e. Visit 5 (3 months +/-1 week from Visit 4):
    i. Subject/Wound evaluation and assessment including measurements (includes local cleansing and debridement if needed, digital image capture and upload to the Burn Unit image storage, manual measurements, and maximal wound depth). This assessment will include status of the wound and if it has closed since Visit 2, wound recurrence and hypertrophic scar formation (measured with modified Vancouver Scar Scale).
    ii. Wound-associated pain assessment
    iii. If the wound(s) remains open, Standard Burn Center wound care treatment
    iv. Collect information on adverse events related to study participation.
    v. Wound cultures

Standard Burn Center Wound Treatment Regimen

- For all groups, change dressing as directed.

- Primary dressings are variable and based on the moisture content, microorganism load and perception of infection. Wound cultures will be taken at every visit. In general, wounds respond differently to various topical treatments. Through our clinical practice, we have found that wounds plateau with the same topical for greater than 4 weeks, hence changing antimicrobial topical helps to manage the bacterial overgrowth. Dressings for both the control group and treatment group include ointment-based dressing and non-ointment-based dressings consisting of silver product. We will start with our application of our slurry, a 1:1:1 ratio of Nystatin ointment, Mupirocin Ointment, and Bacitracin Ointment. This slurry will be applied directly to the cleansed wound, followed by silver gauze and/ or foam product to all wounds. Types of silver product, site and comfort predict use of Restore, Mepilex-AG, or Mepitel-AG. If allergies to the above slurry occurs, we will use medical honey with or without bacitracin. If ointment related rashes present we will transition to silver product only or silver product plus medical honey.
- Secondary dressing: gauze and ace wrap are used to protect wound from shear and desiccation.
- If a patient is allergic to any of the above dressings, alternative dressings will be supplied per standard wound care practice in our clinic.

Table 3. PATIENT STUDY CALENDAR:

	Visit 1 (Screening)	Visit 2 (6 weeks +/- 1 week from last visit)	Visit 3 (6 weeks +/- 1 week from last visit)	Visit 4 (6 weeks +/- 1 week from last visit)	Visit 5 (3 months +/- 1 week from last visit)
Informed Consent	X				
Eligibility	X				
Medical History	X				
Vitals (VAS, HR, BP, RR, O2 Sat, Weight, Height)	X	X	X	X	X
Randomization		X			
Physical Exam	X	X	X	X	X
Pregnancy Test	X[1]				
Injection of pAF (1ml/5cm^2)- Treatment group		X	X		
Burn Center SOC	X	X	X	X	X
Manual Measurement	X	X	X	X	X
Pain Assessment	X	X	X	X	X
Laboratory Tests	X			X	
Wound Culture Swabs	X	X	X	X	X
Digital Image	X	X	X	X	X
Adverse Events Noted		X	X	X	X
Wound assessment	X	X	X	X	X

Follow-up phone call to assess adverse events		X[2]	X[2]		

[1]Only applicable to women of childbearing potential
[2]Follow-up phone call within 24 hours AND 5-7 days after visit to assess adverse events and medications.
Applicable study procedures may be completed via telehealth or by phone, at the discretion of the treating provider.

DRUG DISPENSATION AND RANDOMIZATION:
Upon verification at Visit 2 that the patient's wound is still eligible the patient's largest wound will be randomized to the pAF arm or to the standard-of-care arm, and the CTRM facility will be notified. If the wound is randomized to the pAF arm, the CTRM will package the pAF on dry ice and transport the pAF to the Burn Unit.

The amniotic fluid or investigational product (IP) comes frozen in a nunc cryovial. The frozen IP is thawed at room temperature until the last visible ice crystal is dissolved.

6- ASSESSMENTS

ASSESSMENT OF RESPONSE:
Assessment of response will be performed at every follow up visit.

Wound assessment:

Wound assessments will be performed over the course of 5 exams: Visit 1-screening exam, Visit 2, Visit 3, Visit 4 and Visit 5.

Wound surface area will be calculated. Additionally, maximal length, width and depth of wound will also be measured.

Digital images will be captured at each visit using our image capture software.

The digital photography will be standardized as follows: A ruler will be present in photographs taken at each study visit. Photography will proceed using an iPad camera. We will incorporate a standard background for all photographs to help standardize the iPad's auto color balance. Photos will be taken in normal anatomical positions at a defined distance from the site of interest according to our standard operating procedure. Typically, for best wound image capture flash or direct lights are contraindicated, hence normal clinic room lighting is sufficient. .

Wound digital images will be assessed and evaluated by a University Staff member or contracted professional blinded to both the control and treatment group. Length and width may have substantial variability. Hence, ImageJ software is used to assess area of the wound after the perimeter of the wound is manually outlined (to a reasonable accuracy). It provides more objective assessment of the size of the wound, lending more validity to the wound measurements.

ASSESSMENT OF SAFETY:
Safety and tolerability will be evaluated by the PI and/ or trained physician from the results of reported signs and symptoms and scheduled physical examinations, for every follow-up visit. AEs will also be assessed by phone within 24 hours AND 5-7 days after Visit 2 and Visit 3 (injection visits). Unresolved AEs will be monitored for 1 year. More frequent safety evaluations may be performed if clinically indicated or at the discretion of the investigator. SAEs will be reported within 24 hours of discovery to the central Data Coordinating Center.

7- SAFETY MONITORING

Adverse Event Reporting

The site investigator is responsible for evaluating all adverse events at their Clinical Center and ensuring that they are properly reported. Adverse events that occur during this study will be recorded. The nature of each experience, date and time (where appropriate) of onset, outcome, course, and relationship to treatment will be documented.

Definition of Adverse Event and Serious Adverse Event

Adverse Event (AE) means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)). An event constitutes a disease, a set of related signs or symptoms, or a single sign or symptom.

Serious Adverse Event (SAE): A serious adverse event (SAE) for this population is an adverse event that:

- results in death; or
- is life-threatening (the patient was, in the view of the site investigator, in immediate danger of death from the event as it occurred); or
- requires inpatient hospitalization or prolongs an existing hospitalization; or
- results in persistent or significant disability or incapacity; or
- results in congenital anomaly/birth defect; or
- is any other event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Classification of an Adverse Event (Relatedness, Severity, and Expectedness)

Relatedness: The suspected relationship between study interventions and any adverse event will be determined by the site investigator using the criteria below. Relatedness must be assessed by an investigator and may not be assessed by a research coordinator.

- Not Related: The event is clearly related to other factors, such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

- Possibly Related: The event follows compatible temporal sequence from the time of beginning the assigned study intervention, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.
- Probably Related: The event follows a reasonable temporal sequence from the time of beginning the assigned study intervention, and *cannot be reasonably explained* by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Severity: The severity, which is a measure of intensity, of clinical adverse events and laboratory abnormalities will be recorded by the site investigator and categorized. The following guidelines will be used to describe severity.

- Mild: The event requires minimal or no treatment and does not interfere with the participant's daily activities.
- Moderate: The event results in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- Severe: The event interrupts a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term ``severe" does not necessarily equate to ``serious".

Expectedness of the Event: All adverse events, including serious adverse events, will be evaluated as to whether their occurrence was expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information described for the study intervention. Expected adverse events for this study are:

- ***Infection/ Cellulitis***
- ***Local bleeding***
- ***Purulent drainage***
- ***Inflammation***
- ***Rash***

Treatment or Action Taken: For each adverse event, the site investigator will record whether an intervention was required:

- Medical or surgical procedure
- Concomitant medication: started, changed, or discontinued
- Other, specify
- No action taken

Outcome of Event: Finally, the site investigator will record the clinical outcome of each adverse event as follows:

- Death
- Recovered and the patient returned to baseline status
- Recovered with permanent sequelae
- Symptoms persist

Time Period for Adverse Events
For purposes of this study, events that occur following participant consent through the last study visit will be reported as adverse events. Serious adverse events, unexpected medically attended events, and new onset chronic illnesses will be recorded from consent through Visit 5 (or the last available status before Visit 5 if the subject does not complete Visit 5).

Data Collection Procedures for Adverse Events
After patient consent, all adverse events (including serious adverse events) will be recorded according to relatedness, severity, and expectedness, as well as their duration and any treatment prescribed. Any medical condition present at the time of consent, recorded in the patient's baseline history at study entry, which remains unchanged or improves (unless the clinician feels it is clinically relevant), will not be recorded as an adverse event at subsequent evaluations. However, worsening of a medical condition that was present at the time of consent will be considered a new adverse event and reported.

Adverse events will be coded using the MedDRA coding vocabulary. Coding will be done centrally at the Data Coordinating Center as this requires specific training.

Unanticipated Problems (UP)
Unanticipated problems (UP) are defined as incidents, experiences, or outcomes that are unexpected, related or possibly related to participation in the study, and suggest that the research places subjects at a greater risk of harm than was previously known or recognized. The site investigator will report unanticipated problems to the Data Coordinating Center within 24 hours of becoming aware of the event. A detailed completed report will be required to be sent to the Data Coordinating Center within 3 working days of becoming aware of the event. After receipt of the complete report, the Data Coordinating Center will report these unanticipated problems to the funding Program Official or Project Officer in an expedited manner (as close to 24 hours as possible).

In accordance with local IRB requirements, the site investigator may be required to report such unanticipated problems to the IRB in addition to notifying the Data Coordinating Center. In the event that the medical monitor believes that such an event warrants emergent suspension of enrollment in the trial, and funding staff cannot be reached expeditiously, the Data Coordinating Center will notify the study investigator and all site investigators to cease enrollment in the trial.

Monitoring Serious Adverse Events
A qualified physician will be designated to fulfill the function of the medical monitor for this study. Site investigators and/or research coordinators will report serious adverse events to the Data Coordinating Center within 24 hours of becoming aware of the event. A detailed completed report will be required to be sent to the Data Coordinating Center within 3

working days of becoming aware of the event, and the medical monitor will assess all serious adverse events reported from site investigators.

For each of these serious adverse events, the site investigator will provide sufficient medical history and clinical details for a safety assessment to be made with regard to continuation of the trial. The medical monitor will sign off on each SAE report after review. All SAE reports will be retained at the Data Coordinating Center, and all SAE reports will be available for review by funding staff. The SAE reporting process may be incorporated into the Electronic Data Capture (EDC) System in use for the study.

In the unlikely event that the medical monitor believes an unexpected and study-related SAE warrants emergent cessation of enrollment in the trial, funding staff will be immediately consulted. If these individuals concur with the judgment of the medical monitor, or if the funding staff cannot be reached expeditiously, the Data Coordinating Center will notify the study investigator and all site investigators to cease enrollment in the trial. Resumption of enrollment will not occur without consent of the funding staff.

In accordance with local IRB requirements, the site investigator may be required to report such events to the IRB in addition to notifying the Data Coordinating Center.

Follow-up of Serious, Unexpected and Related Adverse Events
All serious, unexpected and related adverse events, that are unresolved at the time of the patient's termination from the study, will be followed by the site investigators until the events are resolved, subject is lost to follow-up, the adverse event is otherwise explained or has stabilized, or 12 months have passed from the time of last study dose.

PATIENT WITHDRAWAL FROM STUDY:
A subject may withdraw their consent at any time without effect to their care.

DISCONTINUATION OF STUDY DRUG:
pAF-specific treatment will be discontinued if any of the following occur:

- Discovery of new information which makes the subject ineligible to continue participation in the study. This could include systemic sepsis, disseminated infections requiring inpatient hospitalization, worsening infection of the wound, such as necrosis or surgical intervention, increase in wound size by 50% from Visit 2 measurement, development of osteomyelitis, etc.
- Severe allergic reaction possibly related to the investigational product.
- Patient receives any investigational agent/intervention to the wound outside the study visits or is non-compliant with care between Visits 2 and 3.
- Any other condition that in the opinion of the treating physician are not compatible with participation in this study.

The study PI, treating clinicians and research staff will monitor closely for the above events, as well as any additional adverse events that occur while the subject is receiving treatment. Adverse events will be reported immediately upon discovery of the event to the Data Coordinating Center and assessed for seriousness, relatedness, severity, and expectedness.

The DSMB will meet regularly to review adverse events, safety analyses and study data and will have access to the actual treatment assignments for each group.

If study drug is discontinued, we will continue to follow the patient and monitor for safety and efficacy endpoints.

DISCONTINUATION OF STUDY:

The study will be discontinued:

- If any subject has an adverse event leading to respiratory failure requiring resuscitation or death from the investigational product,
- If two or more incidences in the pAF group of wounds require emergent surgical intervention or disseminated infections requiring hospitalization,
- At the discretion of the Data Safety Monitoring Board (DSMB). The DSMB will meet regularly to review adverse events, safety analyses, and study data. The DSMB will have access to the actual treatment assignments for each group.

8- STATISTICAL CONSIDERATIONS

Statistical Method

This is a modest feasibility study with subjects randomized to two groups: (1) treatment group with pAF applied to the randomized wound (n=30 ± 2 patients expected), (2) control group, with wounds receiving standard of care treatment (n=30 ± 2 patients expected).

Feasibility will be demonstrated if the study's clinical wound care providers are able to successfully apply pAF to the wounds in this clinical study situation. Any issues or concerns that occur will be recorded and reported descriptively in a similar fashion to safety outcomes (described below). As no issues or concerns are expected, it should be clear from this descriptive analysis if feasibility of applying pAF is demonstrated.

Primary Endpoint: Whether the patient experienced any post-randomization, study-related SAEs while on study.

For the definition of the primary endpoint, a serious adverse event (SAE) is considered study-related if the medical monitor concludes the SAE is either possibly related or probably related to study participation.

Safety will be assessed by descriptive reporting of the incidence proportion of study-related serious adverse events in each study group, with one-sided 95% binomial exact confidence intervals. No statistical hypothesis test is planned to assess safety, which is consistent even with large Phase III trials. The table below displays the number of subjects, out of 30, experiencing no related SAE and the corresponding lower-bound of the 95% exact confidence interval.

Number of Subjects with no Study-related Serious Adverse Events	Number of Subjects Experiencing any Study-related Serious Adverse Events	Lower-bound of the 95% Exact Binomial Confidence Interval for Safety
30	0	90%
29	1	85%
28	2	80%
27	3	76%

If there are 30 subjects in the pAF group and if all subjects in the pAF group complete the study without experiencing any study-related SAEs, we will be able to state with 95% confidence that the safety of pAF is at least 90%.

Exploratory outcomes for safety include, but are not limited to, the following:

- Whether the patient experienced any post-randomization SAEs while on study (regardless of relatedness to study participation)
- Whether the patient experienced any post-randomization related AEs while on study
- Whether the patient experienced any post-randomization unexpected AEs while on study.

Secondary Endpoint: The percent reduction in wound area at Visit 5 relative to the size at randomization (Visit 2), per the imaging software assessments.

The inclusion criteria limit the study to wounds which are difficult to heal, explaining why patients are not randomized if the wound area shrinks significantly between Visits 1 and 2. Therefore, greater reduction in wound size with pAF, than with SOC will suggest efficacy of pAF for wound treatment. To describe a trend in a statistical hypothesis testing framework, the following two-sided hypothesis will be assessed:

$$H_0: \mu_{pAF} = \mu_{SOC} \text{ versus } H_1: \mu_{pAF} \neq \mu_{SOC}$$

The secondary outcome variable will be the reduction in wound size at Visit 5 relative to the Visit 2 wound size (i.e., 100% * (1- Visit 5 wound area/ Visit 2 wound area)), with all measurements expressed as the approximate area determined by the imaging software. Wound size should be measured at all study visits. To provide an intuitive effect size, percentage change from Visit 2 will be computed at visits 3, 4, and 5 (approximately 6, 12, and 25 weeks after randomization) with the changes at visits 3 and 4 considered as exploratory outcomes. If there are study visits outside of the visit's +/- 1 week window, all percentages will be divided by the number of elapsed days since Visit 2, so the outcome is expressed as a percentage change per day. If the change in wound size at Visit 5 follows a symmetric distribution a two-sample t-test will be performed, otherwise a Wilcoxon rank sum test will be used. As exploratory analyses, the prescribed analytic approach will be applied to the exploratory endpoints of percent reduction in wound area at Visit 3 and percent reduction in wound area at Visit 4.

If enrolled subjects have multiple wounds that meet size requirements (according to the eligibility criteria) the largest wound will be identified as the primary wound, while all others will be identified as target wounds. Data may be collected on the target wounds and used only for exploratory purposes. The largest wound that is randomized to the treatment or standard of care, will be selected as the primary wound for the hypothesis test just described because it is the only wound with randomized treatment; other wounds on the subject are to receive standard-of-care treatment. Data will be collected on the primary wound for analyses. Wounds that are contiguous are treated as one wound. Over the course of the study, if the index wound (i.e., the wound randomized to treatment) becomes contiguous with one or more extant wounds, the "merged" wounds will be regarded as the wound going forward but not retrospectively. It is not anticipated that disconnected wounds will become contiguous over the course of the study.

An exploratory endpoint is whether or not a wound is closed at Visit 5 (the last specified follow-up visit). Fisher's exact test will be used to test for an association between treatment arm and whether the wound is closed at Visit 5.

Descriptive summaries will also be provided by treatment arm for the following additional exploratory endpoints: the proportion of wounds that have recurred at Visit 5; the percent reduction (relative to Visit 2) in the maximal depth of the wound at Visits 3, 4, and 5; the change since Visit 2 in wound-associated pain at Visits 3, 4, and 5; the presence of hypertrophic scar formation at Visit 5 (measured with modified Vancouver Scar Scale); and incidence of wound infection as determined by wound culture/assessment from Visit 4.

The primary analysis of the primary outcome implicitly adopts a last-observation-carried-forward approach. Multiple imputation will be used for the primary analysis of the secondary outcome and may also be used for other outcomes, as described in the Statistical Analysis Plan. Because the sample size is modest, it may not be feasible to use complex multiple imputation models, but candidate variables for the imputation of missing values for the secondary outcome will include variables such as assigned treatment arm and wound area measurements from other study visits. As sensitivity analyses, the analyses of the primary and secondary outcomes will be repeated twice, first replacing each missing outcome with the lowest observed outcome at that timepoint from among subjects in the same assigned treatment arm, and then again replacing each missing outcome with the highest observed outcome at that timepoint from among subjects in the same assigned arm.

A number of additional prespecified exploratory analyses will be conducted. Although the overall sample size is modest, subgroup analyses were requested by the FDA and will be conducted for the primary and secondary outcomes using subgroups defined by the following variables: sex; race; ethnicity; diagnosis of diabetes mellitus or a screening hemoglobin A1C greater than or equal to 6.5; use of immunosuppressive medications; presence/absence of known malignancy other than non-metastatic basal or squamous cell carcinoma; nutritional status as defined by albumin levels; presence/absence of blood coagulation conditions defined by PT/INR and PTT levels; presence/absence of venous vascular disease affecting the wound area; presence/absence of arterial vascular disease affecting the wound area; Visit

1 oxygen saturation <90% or ≥ 90%; and concomitant anticoagulation medication or lack thereof. The details of the subgroup analysis will be available in the Statistical Analysis Plan (SAP).

Finally, although some additional collected data elements may influence the response, the primary and secondary analyses will not adjust for these other characteristics because the modest sample size makes such adjustments impractical. The randomization procedure will be relied upon to avoid favoring either treatment arm in the safety and efficacy comparisons. Exploratory analyses may be conducted to attempt to adjust for one or more additional variables.

Sample Size Justification

A sample size of n = 30 patients per group (total n = 60) is expected, though this may differ slightly because of the randomization procedure. Thirty participants in the pAF group with no related serious adverse events will provide a lower-bound of the 95% one-sided exact binomial confidence interval for safety of 90% and provide enough evidence to move on to the next phase of study.

9 - DATA MANAGEMENT

Clinical Site Data Management

The Data Coordinating Center (DCC) will develop an electronic data capture system for this trial. Currently the DCC uses multiple applications, such as OpenClinica or REDCap, and will elect to use the most appropriate application at the time of implementation of the study.

The DCC will use an electronic discrepancy management system to notify sites of inconsistent or erroneous data entry, which will be corrected by the clinical site. The discrepancy management system maintains an audit trail of all discrepancy resolution.

Study Monitoring

The investigators recognize the importance of ensuring data of excellent quality. Study monitoring is critical to this process. Monitoring has been a very effective tool for maintaining data quality in previous network studies, and we will utilize this process to ensure excellent quality data in the proposed study. The DCC utilizes risk-based methodology to identify and correct problems that may arise at sites. The risk-based approach to monitoring focuses on oversight activities and preventing or mitigating key risks to data quality, as well as to processes critical to human subject protection and integrity of the trial or study.

Study monitors must be provided with appropriate access to study materials and the medical records for study subjects. If the medical records are in electronic form, the clinical investigator or an authorized individual must provide any assistance necessary to facilitate the study monitor's review of data in the electronic medical record.

Site Monitoring Plan

A supplemental study-specific risk-based monitoring plan, separate from the protocol will be completed which outlines specific criteria for monitoring. This plan may include the number of planned site visits, criteria for focused visits, additional visits or remote monitoring, a plan for chart review and a follow up plan for non-compliant sites. The monitoring plan also describes the type of monitoring that will take place (e.g., sample of all subjects within a site; key data or all data), the schedule of visits, how they are reported and a time frame to resolve any issues found.

Clinical Site Monitoring

Site monitoring visits will be performed by a trained site monitor during the study period to ensure regulatory compliance, patient safety, and to monitor the quality of data collected. Essential document binders, regulatory documents and data collection forms may be reviewed. Interim visits will take place depending on grant budget, site enrollment, and compliance issues identified. The site monitor will provide each site with a written report, and sites will be required to follow up on any deficiencies. It is anticipated that the study monitoring visits for this protocol will consist of a site initiation visit (prior to patient enrollment), interim visits, and a close-out visit. The site initiation may take place as group training made up of site investigators and research assistants.

Remote Monitoring

The Data Coordinating Center may supplement on-site monitoring with remote monitoring activities. Remote monitoring involves detailed review of the data entered by the site and consultations with the site investigator and/or research coordinator to review safety and data quality. This may require uploading copies of medical records, patient study files, regulatory documentation, or other source documents for the monitor to review. Alternatively, other methods, such as remotely viewing source documentation, may be utilized. This helps assure protocol compliance and accurate data collection. The Data Coordinating Center may conduct more remote monitoring activities early in the trial to assure protocol compliance and identify any training issues that may exist. Remote monitoring documents will be retained in accordance with federal requirements.

10 - PROTECTION OF HUMAN SUBJECTS

Institutional Review Board Approval

The Data Coordinating Center and each clinical center must obtain approval from their respective IRBs prior to participating in the study. The Data Coordinating Center will track IRB approval status at all participating centers and will not permit subject enrollment without documentation of initial IRB approval and maintenance of that approval throughout subsequent years of the project.

Amendments

Any amendments or administrative changes to the IRB approved protocol will not be initiated without submission of an amendment for IRB review and approval.

Any amendment to the protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study are required to submit the amendment for FDA review.

Annual Reports

An annual progress report will be submitted to the FDA within 60 days of the anniversary of the date that the IND went into effect (21 CFR 312.33)

Informed Consent

Informed consent is required because all eligible subjects are at least 18 years old. Subjects who are capable of giving consent and who are alert and competent, will be asked, following an appropriate discussion of risks and benefits, to give consent to the study. For those with diminished mental capacity, a Legal Authorized Representative will be used.

Potential Risks

Loss of confidentiality of the subject is a potential risk of the study; however, safeguards are in place to protect against this. There is an additional medical risk of rash around the injection site if randomized to pAF treatment.

Protection Against Potential Risks

Regarding loss/breach of privacy and confidentiality, all applicable parties (e.g. clinical sites, DCC) will be responsible for ensuring that appropriate data security procedures are in place.

Potential Benefits

There may be a potential benefit in helping decrease the size of wounds that are treated with pAF and the amount of time it takes to decrease the wound size.

11 - REGULATORY CONSIDERATIONS

Food and Drug Administration

This trial is being conducted under an Investigational New Drug application. The clinical investigator at each participating site will complete a Form FDA 1572, ``Statement of Investigator."

Health Insurance Portability and Accountability Act

Data elements collected include the date of birth and date of visits. Prior to statistical analyses, dates will be used to calculate patient age at the time of the study events. The final data sets (used for study analyses and made available at the end of the study) will be de--identified, and will exclude these specific dates.

Data elements for race, ethnicity, and gender are also being collected. These demographic data are required for Federal reporting purposes to delineate subject accrual by race, ethnicity, and gender.

Inclusion of Women and Minorities
There will be no exclusion of patients based on gender, race, or ethnicity.

12- DATA COORDINATING CENTER

Overview
The Data Coordinating Center (DCC) in the Department of Pediatrics at the University Of Utah School Of Medicine provides data coordination and management services for a variety of national research networks. Anchoring these services is a new state-of-the art, energy efficient data center. The data center facility supports more than 3500 users around the country and provides a secure, reliable, enterprise-wide infrastructure for delivering mission critical DCC systems and services.

Facility, Hardware, Storage, Data Backup and System Availability
The data center was built using high industry standards and energy efficient cooling solutions. The data center is cooled by a LCP (Liquid Cooling Package) inline cooling technology; providing efficiency, redundancy and the modularity required. Cooling is based upon a hot/cold aisle design that allows for even air distribution with minimal hot spots. The data center electrical power system contains an uninterruptible power system (UPS) with a diesel backup generator. The data center is protected with a FM200 fire suppression system to act as a secondary system to the smoke detectors. The data center provides enhanced security to safeguard the equipment and the data within it. Entry into the data center is restricted by card access and layered security measures and controls. The data center and external building access points are monitored with video surveillance.

The data center has a virtualized environment. The virtualized environment consists of more than 400 virtual servers and nearly 25 physical servers. The data center's virtualized solution provides key advantages; 1) high availability – in the event of hardware failure, virtual servers automatically go back online in a seamless process. 2) Flexible infrastructure – disk storage, memory and processor capacity can be increased or reallocated at any time. 3) Rapid deployment – servers can be provisioned on demand.

Production servers running mission critical applications are clustered and configured for failover events. Servers are backed up with encryption through a dedicated backup server. Our storage area networking (SAN) applications, clusters, and switch-to-switch links are on a 10 gigabit network. Incremental backups occur Monday through Friday. A full system backup occurs weekly. Full backups are taken off site on a weekly basis to an off-site commercial storage facility. The data center currently manages over 150 terabytes of data.

Our information systems are available 24 hours a day, 7 days a week to all users, unless a scheduled maintenance interruption or mitigation of an unexpected event is required. If this occurs, we notify all users of the relevant systems, and data entry can be deferred until after the interruption is over.

Security, Support Encryption and Confidentiality

The data center coordinates the network infrastructure and security with the University Information Technology (UIT) at the University of Utah. This provides us with effective firewall hardware, automatic network intrusion detection, and the expertise of dedicated security experts working at the University. Centralized authentication and communication over public networks is encrypted using transport layer security (TLS) or virtual private network (VPN) technologies, both of which provide at least 128 bit encryption.

All network traffic is monitored for intrusion attempts, security scans are regularly run against our servers, and our IT staff are notified of intrusion alerts. Security is maintained with Windows user/group domain-level security. Users are required to change their passwords every 90 days. All files are protected at user/group levels; database security is handled in a similar manner with group-level access to databases, tables, and views in Microsoft SQL Server. Finally, all laptop computers in use in the DCC are whole-disk encrypted.

The data center uses control center tools to continuously monitor systems and failure alerts. Environmental and network systems are also monitored to ensure up time. And highly trained system administrators on staff are available to respond in high risk emergency events.

All personnel involved with the DCC have signed confidentiality agreements concerning data encountered in the course of their daily work. All personnel (including administrative staff) have received Human Subjects Protection and Health Information Portability and Accountability Act (HIPAA) education. We require all users to sign specific agreements concerning security, confidentiality, and use of our information systems, before access is provided.

Record Access

The medical record and study files (including informed consent) must be made available to authorized representatives of the Data Coordinating Center, upon request, for source verification of study documentation. In addition, medical information and data generated by this study must be available for inspection upon request by representatives (when applicable) of the Food and Drug Administration (FDA), NIH, other Federal funders, and the Institutional Review Board (IRB) for each study site.

13 - APPENDICES

APPENDIX A- REFERENCES

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